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PATENT & TRADEMARK OFFICE

Attorney Docket No. 01626C/HG

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of	:	Takashi FUJITA et al.
Serial No.	:	09/991,100
Filed	:	November 21, 2001
For	:	THIAZOLIDINE-2,4-DIONE HYDROCHLORIDE SALT, PHARMACEUTICAL COMPOSITIONS THEREOF AND TREATMENT METHOD THEREWITH
Art Unit	:	1626
Examiner	:	Laura Lynne Stockton

SECOND DECLARATION UNDER 37 CFR 1.132

Dr. Kazushi ARAKI declares that he obtained his D.V.M. degree in Veterinary medicine from Tokyo University of Agriculture and Technology in 1992 and obtained his Ph.D. in 1996 from Tokyo University. His Ph.D. research was Meiotic abnormalities of c-mos knockout mouse oocytes : activation after first meiosis or entrance into third meiotic metaphase.

He joined Sankyo in 1996. He is now an Associate Chief Researcher in Pharmacology & Molecular Biology res. labs. in Sankyo. His research interests are antidiabetic mechanism of insulin sensitizer in diabetic animal model; characterization of diabetic animal models and pharmacology of antidiabetic drugs.

In order to show that the activity of the claimed salt form of the compound when used in the claimed method provides

surprisingly superior results, additional comparative data was obtained under his supervision and control. This data is presented in the following:

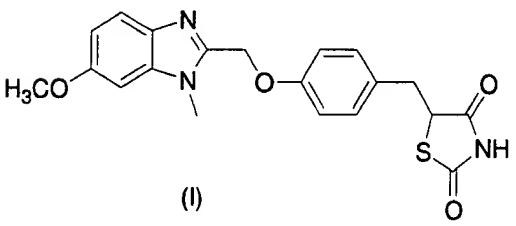
As shown below, two kinds of additional data are presented in order to explain the invention's effect more clearly. Thereafter, there is a discussion of the additional data together with the prior data, which was shown in this application and the previous Declaration. Finally, the expectations of the art, based on the art of record, are established.

Test 1

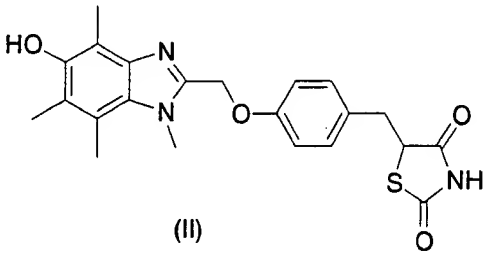
Solubility test

Test compounds

Two compounds which have a structure of formula (II) are used.



(I)



(II)

In the case of the compounds of formula (II), its hydrochloride salt and free form are called Compound C and

Compound D respectively. Compound C and D are from the cited Fujita patent and these are disclosed with physical properties. (Compound C is Example 4 and Compound D is Example 3 in the patent.)

In the case of the compounds of formula (I), its hydrochloride salt and free form are called Compound A and Compound B respectively. Compound A is the hydrochloride salt claimed in this application.

One of the reasons why Compound C and D were chosen is that Compound C is the only hydrochloride compound prepared in the Fujita patent. In addition, the structure of those compounds is similar to that of Compound A. For instance the structural difference of the comparative Compound C and D from Compound A is only at the substituent groups on the benzimidazole moiety.

Above mentioned 4 compounds (compound A, B, C and D) are the same compounds' definition as those in the previous Declaration.

Test Methods

Solubility test have been done. This test method is same as described in the present application.

Test Example

To 100 ml of the 1st fluid of Japanese Pharmacopeia (1000 ml solution made by mixing 2.0 g of sodium chloride with 7.0 ml of hydrochloric acid and water) were added 25 mg of Compound C or Compound D, and the mixture was stirred with a stirrer at 37°C in a 200 ml Erlenmeyer flask. One hour later, 10 ml of the sample were filtered through Acrodisk LC 13 (PVDF, manufactured by German Science Co.). The initial 3 ml were discarded, and the following 7 ml were taken into a test tube. Of this sample, 5 ml were taken accurately with a whole pipette and added to 2 ml of methanol accurately measured in advance in a test tube.

The quantity was measured by HPLC and the solubility was decided from a calibration curve made according to the following procedure.

The calibration curve was made by preparing a methanolic standard solution of Compound D at a concentration of 200 µg/ml, 40 µg/ml and 10 µg/ml, mixing each 2 ml of the standard solution with 5 ml of the 1st fluid of Japanese Pharmacopeia and determined by HPLC.

HPLC Condition:

Analytical column: L-column ODS (4.6 mm IDx15 cm, manufactured by Chemicals Evaluation Research Institute Japan)

Mobile phase: 0.01 mol/L acetic acid buffer solution (pH 5.0)/acetonitrile mixture (13: 7) Flow rate: about 1.0 ml/min.

Column temperature: 40°C.

Detector: ultraviolet absorptiometer (measuring wavelength: 290 nm)

Comparative Test Results

The comparative test data are as shown below.

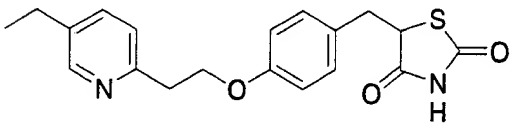
Table 1

	0 Hour	Solubility 1.0 hour later (μg/mL)
Compound D	0	46.4
Compound C	0	148

Test 2

Relationship between plasma glucose lowering rate and plasma glucose.

Test compounds



HCl

Pioglitazone hydrochloride

Pioglitazone is the compound of Example 1 in USP No. 4,687,777.

As shown above, Pioglitazone hydrochloride is used as a test compound. Pioglitazone hydrochloride is a therapeutic agent for diabetes named "Actos" from Takeda Chemical Industries, Ltd. One of the reasons why it was chosen is that it has the same glucose lowering machanism as compound A. And the other reason is that this compound has the same specific structure of benzylthiazolidinedione skeleton, as that of Compound A.

Test Methods

Hypoglycemic test and Plasma concentration test have been done.

Test Example

1. Hypoglycemic action

On day 0, the blood sample was collected from the tail vein of each KK mouse (4-5 month old) which developed diabetes and the plasma glucose level was measured after centrifugation. These mice were then classified into 7 groups (6 mice per group). For seven days, powdered food (F-2, Funabashi Farm) which contains the test compound at adjusted concentrations of 0.0001%, 0.0003%, 0.001%, 0.003%, 0.01%, and 0.03% (Pioglitazone hydrochloride) was given to mice. The mouse group given the test compound refers to "the medicine administered group", and that given the powdered food containing free of the test compound refers to "the control".

On day 7, the blood sample was collected from the tail vein of each mouse and the plasma glucose level was measured by a glucose analyzer ("Glucoloader-GXT", A&T Inc.). The plasma glucose lowering rate was calculated using the following equation:

Plasma glucose lowering rate (%)=

(average plasma glucose level of the control - average plasma glucose level of the medicine administered group) X 100 / the plasma glucose level of the control

At the end of experiment, the mice were killed by decapitation and the blood samples were collected for measurement of plasma pioglitazone concentration.

2. Analytical methods for the measurement of plasma concentration

1) Preparation of analytical samples from plasma samples

The plasma sample (30 µl) was mixed well with 30 µl of the internal standard (I.S.) solution containing a proper compound and 60 µl of methanol in 1.5 ml plastic tube and centrifuged at 15,000 rpm for 10 min at 4°C. The supernatant obtained was used for measurement of Pioglitazone by HPLC.

2) Samples for calibration curve and quality control (QC)

The control plasma (30 µl) was mixed well with 30 µl of the standard solution, 30 µl of the I.S. solution and 30 µl of methanol in 1.5 ml plastic tube. The samples were processed as described above. The concentrations of the calibration

standard samples were 0.0391, 0.0781, 0.156, 0.313, 0.625, 1.25, 2.50, 5.00, 10.0 and 20.0 μg/ml as Pioglitazone concentrations.

The concentrations of the QC samples were 0.0781, 1.25 and 20.0 μg/ml as Pioglitazone concentrations.

3) HPLC analysis

The conditions for HPLC analysis were as follows.

HPLC apparatus: LC-10Avp (Shimazu Corp.)

Column: YMC-Pack ODS-A-312 (150x6.0 mm ID, S-5 mm, YMC Co., Ltd.)

Column temperature: 35°C

Flow rate: 1.0 ml/min

UV detection: 225 nm

Mobile phase: CH_3CN: H_2O: Triethylamine: CH_3COOH = 35:65:0.1:0.1 (v/v)

Injection volume: 30 μl

4) Standard curve for Pioglitazone in plasma

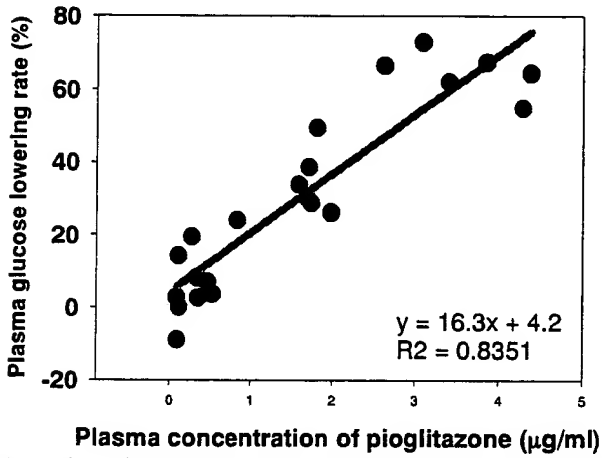
Standard curves of the nominal concentration against the peak areas of Pioglitazone to the I.S. were fitted by the least-squares linear regression method ($y = ax+b$, weight: $1/y^2$) using the computer software Millennium32 (Nihon Waters K.K.). The limit of quantitation was defined as the minimum concentration having accuracy within ± 20%. The QC samples, prepared in duplicate at each of three concentration of Pioglitazone described above were used to evaluate

intra-assay reproducibly. The plasma concentrations of Pioglitazone were calculated using the above standard curve.

Test Results

The relationship between plasma concentration and plasma glucose lowering rate is as shown below.

Graph 1



(R2 value indicates linearity of the relationship. When the value is closer to 1, the linearity is higher.)

Discussion

In order to discuss the above data together with the prior data, the solubility data and the glucose lowering rate data are collected together and presented below.

Solubility test results

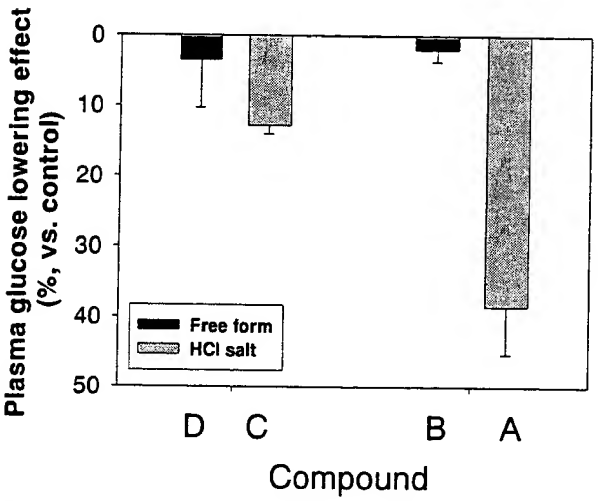
Table 2

	0 Hour	Solubility 1.0 hour later (μg/mL)
Compound B	0	41.0
Compound A	0	86.4
Compound D	0	46.4
Compound C	0	148

(Data of compound A and B are quoted from Table 2 of instant application. Data of compound C and D are quoted from Table 1 of this argument.)

Hypoglycemic activity test results

Graph 2



(Graph 2 is quoted from the previous Declaration.)

From Table 2, both compounds show the solubility increasing effect by salt forming, however, all 4 compounds still show poor solubility. So that the compounds, which show solubility rate like Table 2, are classified as the poor soluble compound. Because a series of compounds, which have benzylthiazolidine skeleton, show the same tendency of solubility, all of them would be classified as the poor soluble compounds.

Regarding series of poor soluble compounds, Shargel et al. (Encyclopedia of Pharmaceutical Technology Second Edition Vol.1, p. 156-176, 2002) on page 167, columns 1, states, "In biologic systems, drug dissolution in an aqueous medium is an important prior condition of systemic absorption. The rate at

which drugs with poor aqueous solubility dissolve from an intact or disintegrated solid dosage form in the GI tract often controls the rate of systemic absorption of the drug." In other words, the solubility of poor soluble compounds have a correlation between the solubility and the blood concentration. Therefore when solubility of the compound increases by salt forming, blood concentration of it should also increase (see enclosed copy).

Moreover it is well known that a series of compounds, which posses a same specific skeleton and a same bioactivity mechanism, has same correlation between its blood concentration and its bioactivity rate. Graph 1 shows almost linear relationship between blood concentration and plasma glucose lowering rate according to its R2 value. Therefore, this data also supports the expectation that in the series of these compounds that there is a linear correlation between their plasma glucose lowering rates and their blood concentrations.

In the case of C and D in Table 1, there is a solubility data of compound C that shows nearly 3 times higher than its free form compound D. According to the relationship between blood concentration and solubility as mentioned above, the improving effect of blood concentration, which is expected from the solubility result, should be 3 times. Then at plasma glucose lowering rate of Graph 2, the improving effect due to

salt forming is approximately 3 times. Because C and D exist as the same free form D in the blood, this data also support the expectation of a linear correlation between blood concentration and plasma glucose lowering rate of these compounds.

Based on the above, it is submitted that one skilled in the art at the time of invention would expect that solubility and plasma glucose lowering rate would correlate in the case of the compounds, which have benzyltiazolidine skeleton and insulin sensitize action. This would lead to the expectation from the solubility data of A (Table 2) that there would be and improving effect of 2 times by salt forming: Because A and B exist as the same freeform B in the blood, if solubility becomes 2 times higher, the bioactivity should become 2 times stronger.

By contrast, the activity of Compound A is about twenty times stronger than that of its free form compound B at the plasma glucose lowering rate (Graph 2). It is submitted that, from the above mentioned reference and common knowledge, this salt forming effect of hydrochloride salt is far stronger than that which could have been expected. Therefore one skilled in the art at the time of the invention would not have expected this specific improving effect of the salt.

Further to above information, Berge et al. teach that it could be generally expected to prepare the salt of known

compounds with increasing physicochemical properties such as solubility and hygroscopicity. Moreover Berge et al. on page 16, columns 1, states, "At present, selecting a salt form that exhibits the desired combination of properties is a difficult semiempirical choice." Therefore, as described in the previous Declaration, Berge et al. does not teach or suggest concrete improving activity effect that would be expected to prepare hydrochloride salt of the known compounds such as the compounds within the scope of the reference patent.

In view of above data and knowledge, the salt forming effect of instant claimed hydrochloride salt is far stronger than that would have been expected for this kind of compounds. Therefore one skilled in the art at the time of the invention would not have expected this specific effect of the salt.

In conclusion, Compound A shows an unexpected bioactivity improving effect compared to the compounds within the broad scope of the reference patent.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, of Title 18 of the United States Code and that such willful false

statements may jeopardize the validity of the application or any patent issued thereon.

Date:_____

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Kazushi ARAKI

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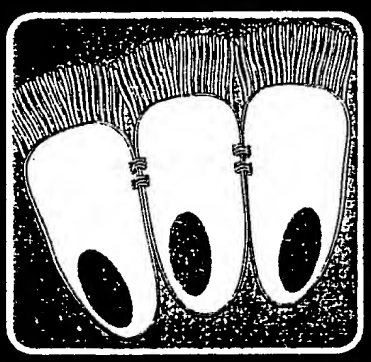
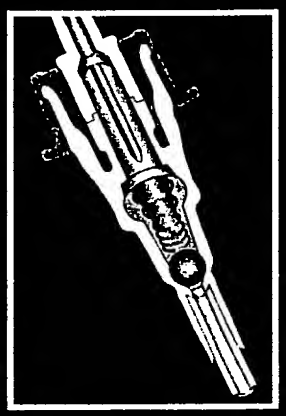
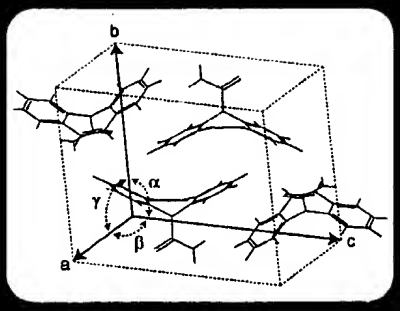
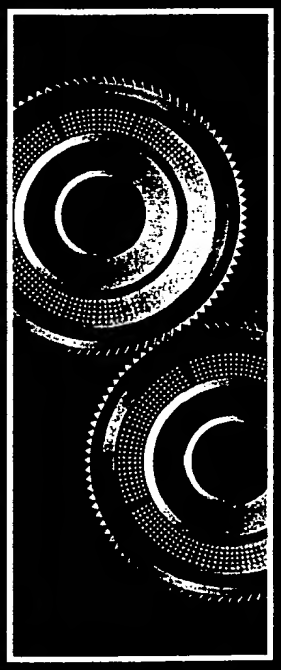
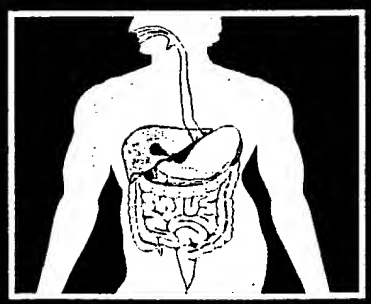
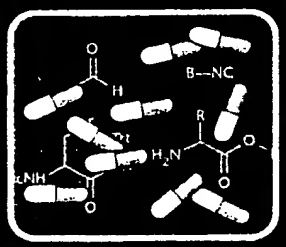
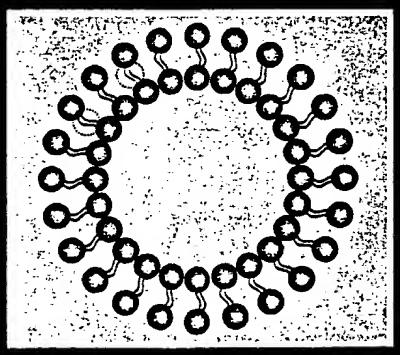
Encyclopedia of Pharmaceutical Technology

Second Edition

Volume I



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BIOPHARMACEUTICS

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INTRODUCTION

Biopharmaceutics is the study of the interrelationship of the physicochemical properties of the drug [active pharmaceutical ingredient, (API)] and the drug product (dosage form in which the drug is fabricated) based on the biological performance of the drug (Table 1).

Biopharmaceutics also considers the impact of the various manufacturing methods and technologies on the intended performance of the drug product. Biopharmaceutics uses quantitative methods and theoretical models (1) to evaluate the effect of the drug substance, dosage form, and routes of drug administration on the therapeutic requirements of the drug and drug product in a physiological environment.

Bioavailability is often used as a measure of the biological performance of the drug and is defined as a measure of the rate and extent (amount) to which the active ingredient or active moiety becomes available at the site of action. Bioavailability is also a measure of the rate and extent of therapeutically active drug that is systemically absorbed.

Biopharmaceutics allows for rational design of drug products to deliver the drug at a specific rate to the body in order to optimize the therapeutic effect and minimize any adverse effects. As shown in Table 1, biopharmaceutics is based on the physicochemical characteristics of the active drug substance, the desired drug product, and considerations of the anatomy and physiology of the human body (1). Inherent in the design of a suitable drug product is knowledge of the pharmacodynamics of the drug, including the desired onset time, duration, and intensity of clinical response, and the pharmacokinetics of the drug including absorption, distribution, elimination, and target drug concentration.

Thus, biopharmaceutics involves factors that influence the: 1) protection and stability of the drug within the drug product; 2) the rate of drug release from the drug product; 3) the rate of dissolution of the drug at the absorption site; and 4) the availability of the drug at its site of action (Fig. 1).

[a]The content in this article reflects the view of the authors and does not represent the view of FDA.

BIOPHARMACEUTIC CONSIDERATIONS IN DRUG PRODUCT DESIGN

Drugs are generally given to a patient as a manufactured drug product (finished dosage form) that includes the active drug and selected ingredients (excipients) that make up the dosage form. Common pharmaceutical dosage forms include liquids, tablets, capsules, injections, suppositories, transdermal systems, and topical drug products. The formulation and manufacture of a drug product requires a thorough understanding of the biopharmaceutics.

Each route of drug application presents special biopharmaceutic considerations in drug product design (Table 2). Systemic drug absorption from an extravascular site is influenced by the anatomic and physiologic properties of the site and the physicochemical properties of the drug and the drug product. The anatomy, physiology, and the contents of the gastrointestinal tract (GI) are considered in the design of a drug product for oral administration. For example, considerations in the design of a vaginal tablet formulation for the treatment of a fungus infection include whether the ingredients are compatible with vaginal anatomy and physiology, whether the drug is systemically absorbed from the vagina and how the vaginal tablet is to be properly inserted and placed in the appropriate area for optimum efficacy. Requirements for an eye medication include pH, isotonicity, sterility, local irritation to the cornea, draining of the drug by tears, and concern for systemic drug absorption. An additional consideration might be the contact time of the medication with the cornea. Although, increased eye contact time might be achieved by an increase in viscosity of the ophthalmic solution, the patient may lose some visual acuity when a viscous product is administered. Biopharmaceutic considerations for a drugs administered

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Table 1 Biopharmaceutic considerations in drug product design

Active pharmaceutical ingredient (API)		
	Stability	Impurities
	Solubility	Salt form
	pH and pKa	Particle size
	Crystalline form (polymorph)	Complexation
	Excipient interaction and compatability	
Drug product		
	Type of drug product (capsule, tablet, solution, etc.)	Stability
	Immediate or modified release	Excipients
	Dosage strength	Manufacturing variables
	Bioavailability	
Physiologic factors		
	Route of administration	Blood flow
	Permeation of drug across cell membranes	Surface area
	Binding to macromolecules	Biotransformation
Pharmacodynamic and pharmacokinetic considerations		
	Bioavailability	Pharmacokinetics
	Therapeutic objective	Dose
	Adverse reactions	Toxic effects
Manufacturing considerations		
	Production methodology and technology	Cost
	Quality control/quality assurance	Stability testing
	Specification of raw materials	
Patient considerations	Compliance, labeling, and product acceptance	Cost

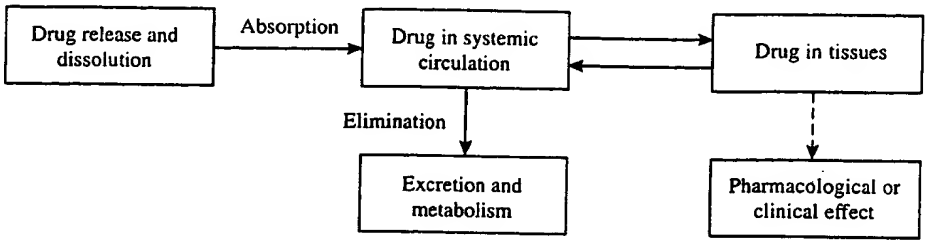

Fig. 1 Scheme demonstrating the dynamic relationships among the drug, the product, and pharmacologic effect. (From Ref. 1.)

by intramuscular injection include, local irritation, drug dissolution, and drug absorption from the injection site.

Biopharmaceutic studies may be performed using in vitro or in vivo methods (Table 3). In vitro methods are useful (2–6) to understand the physico-chemical properties of the drug and drug product and to evaluate the quality of the manufacturing process. Ultimately, the drug must be studied in vivo, in humans to assess drug efficacy, including the pharmacodynamic, pharmacokinetic, therapeutic and toxic profiles. Drug dissolution, absorption, metabolism, and potential interaction with food and other components in the GI tract are major biopharmaceutic topics for research and regulatory considerations in drug development.

A drug given by intravenous administration is considered complete or 100% bioavailable because the drug is placed directly into the systemic circulation. By carefully choosing the route of drug administration and proper design of the drug product, drug bioavailability can be varied from rapid and complete systemic drug absorption to a slow, sustained rate of absorption or even virtually no absorption, depending on the therapeutic objective. Once the drug is systemically absorbed, normal physiologic processes for distribution and elimination occur, which usually is not influenced by the specific formulation of the drug. The rate of drug release from the product, and the rate of drug absorption, are important in determining the onset, intensity, and duration of drug action of the drug.

RATE-LIMITING STEPS IN ORAL DRUG ABSORPTION

Systemic drug absorption from a drug product consists of a succession of rate processes (Fig. 2). For solid oral, immediate release drug products (e.g., tablet, capsule), the rate processes include 1) disintegration of the drug product and subsequent release of the drug; 2) dissolution of the drug in an aqueous environment; and 3) absorption across cell membranes into the systemic circulation. In the process of drug disintegration, dissolution, and absorption, the rate at which drug reaches the circulatory system is determined by the slowest step in the sequence.

The slowest step in a kinetic process is the rate-limiting step. Except for controlled release products, disintegration of a solid oral drug product is usually more rapid than drug dissolution and drug absorption. For drugs that have very poor aqueous solubility, the rate at which the drug dissolves (dissolution) is often the slowest step, and therefore exerts a rate-limiting effect on drug bioavailability. In contrast, for a drug that has a high aqueous solubility, the dissolution rate is rapid and the rate at which the drug crosses or permeates cell membranes is the slowest or rate-limiting step.

PHYSIOLOGIC FACTORS AFFECTING DRUG ABSORPTION

Passage of Drugs Across Cell Membranes

For systemic absorption, a drug must pass from the absorption site through or around one or more layers of cells to gain access into the general circulation. The permeability of a drug at the absorption site into the systemic circulation is intimately related to the molecular structure of the drug and the physical and biochemical properties of the cell membranes. For absorption into the cell, a drug must traverse the cell membrane. Transcellular absorption is the process of a drug movement across a cell. Some polar molecules may not be able to traverse the cell membrane, but instead, go through gaps or "tight junctions" between cells, a process known as paracellular drug absorption. Some drugs are probably absorbed by a mixed mechanism involving one or more processes.

Passive diffusion

Passive diffusion is the process by which molecules spontaneously diffuse from a region of higher concentration to a region of lower concentration. This process is passive because no external energy is expended. Drug

Table 2 Common routes of drug administration

Route	Bioavailability	Advantages	Disadvantages
Parenteral routes			
Intravenous bolus (IV)	Complete (100%) systemic drug absorption. Rate of bioavailability considered instantaneous.	Drug is given for immediate effect.	Increased chance for adverse reaction. Possible anaphylaxis.
Intravenous infusion (IV inf)	Complete (100%) systemic drug absorption. Rate of drug absorption controlled by infusion pump.	Plasma drug levels more precisely controlled. May inject large fluid volumes. May use drugs with poor lipid solubility and/or irritating drugs.	Requires skill in insertion of infusion set. Tissue damage at site of injection (infiltration, necrosis, or sterile abscess).
Intramuscular injection (IM)	Rapid from aqueous solution. Slow absorption from nonaqueous (oil) solutions.	Easier to inject than intravenous injection. Larger volumes may be used compared to subcutaneous solution.	Irritating drugs may be very painful. Different rates of absorption depending upon muscle group injected and blood flow.
Subcutaneous injection (SC)	Prompt from aqueous solution. Slow absorption from repository formulations.	Generally, used for insulin injection.	Rate of drug absorption depends upon blood flow and injection volume.
Enteral Routes			
Buccal or sublingual (SL)	Rapid absorption from lipid-soluble drugs.	No "first-pass" effects.	Some drug may be swallowed. Not for most drugs or drugs with high doses.
Oral (PO)	Absorption may vary. Generally slower absorption rate compared to IV bolus or IM injection.	Safest and easiest route of drug administration. May use immediate-release and modified-release drug products.	Some drugs may have erratic absorption, be unstable in the gastointestinal tract, or be metabolized by liver prior to systemic absorption.
Rectal (PR)	Absorption may vary from suppository. More reliable absorption from enema (solution).	Useful when patient cannot swallow medication. Used for local and systemic effects.	Absorption may be erratic. Suppository may migrate to different position. Some patient discomfort.
Other routes			
Transdermal	Slow absorption, rate may vary. Increased absorption with occlusive dressing.	Transdermal delivery system (patch) is easy to use. Used for lipid-soluble drugs with low dose and low MW.	Some irritation by patch or drug. Permeability of skin variable with condition, anatomic site, age, and gender. Type of cream or ointment base affects drug release and absorption.
Inhalation	Rapid absorption. Total dose absorbed is variable.	May be used for local or systemic effects.	Particle size of drug determines anatomic placement in respiratory tract. May stimulate cough reflex. Some drug may be swallowed.

(From Ref. 1.)

Table 3 Examples of in vitro and in vivo biopharmaceutic studies

Biopharmaceutic studies (in vivo)	Bioavailability study	Measurement of drug in plasma, urine or other tissues
	Acute pharmacologic effect	Measurement of a pharmacodynamic effect, e.g., FEV_1, blood pressure, heart rate, skin blanching
	Clinical study	Measurement of drug efficacy
Biopharmaceutic studies (in vitro)	Drug release/dissolution	Measurement of the rate of drug dissolved under specified conditions
	Drug permeability	Use of CACO2 cells (an isolated colon cell line) are grown into membranes to study the intestinal permeability and gut metabolism of drugs.
	Drug biotransformation (metabolism)	Use of liver cells, homogenates or isolated cytochrome P450 isozymes to drug study biotransformation.

molecules move randomly forward and back across a membrane (Fig. 3). If the two regions have the same drug concentration, forward-moving drug molecules will be balanced by molecules moving back, resulting in no net transfer of drug. For a region that has a higher drug concentration, the number of forward-moving drug molecules will be higher than the number of backward-moving molecules, resulting in a transfer of molecules to the region with the lower drug concentration, as indicated by the big arrow. Flux is the rate of drug transfer and is represented by a vector to show its direction. Molecules tend to move randomly in all directions because molecules possess kinetic energy and constantly collide with each another in space. Only left and right molecule movements are shown in Fig. 3, because movement of molecules in other directions would not result in concentration changes because of the limitation of the container wall.

Passive diffusion is the major transmembrane process for most drugs. The driving force for passive diffusion is the difference in drug concentrations on either side of the cell membrane. According to Fick's Law of Diffusion, drug molecules diffuse from a region of high drug concentration to a region of low drug concentration

$$dQ/dt = \{DAK/h\}(C_{GI} - C_p)$$

where dQ/dt = rate of diffusion; D = diffusion coefficient; K = partition coefficient; A = surface area

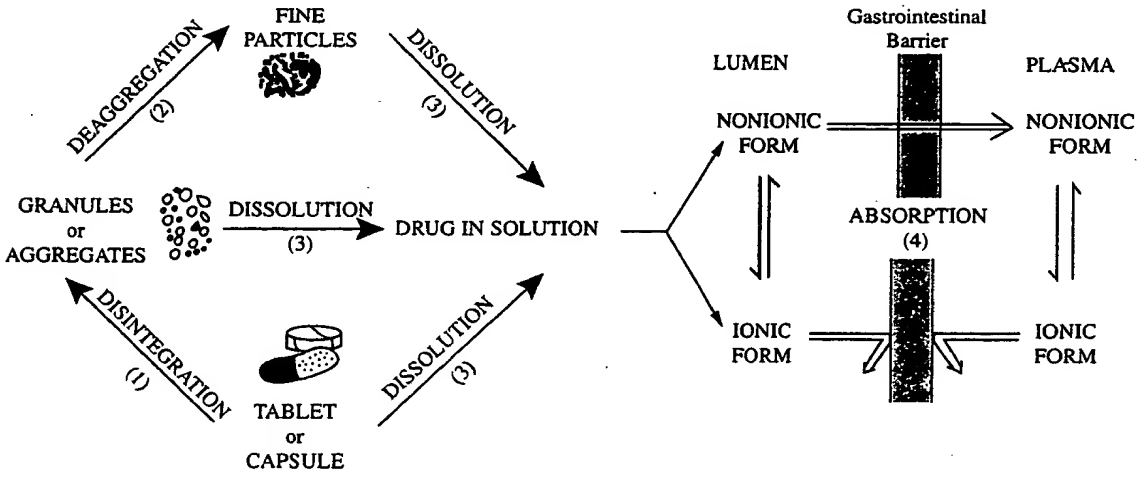

Fig. 2 Summary of processes involved following the oral administration of a drug in tablet or capsule form. (From Blanchard, J. Gastrointestinal absorption. II. Formulation factors affecting bioavailability. Am. J. Pharm. **1978**, *150*, 132–151.)

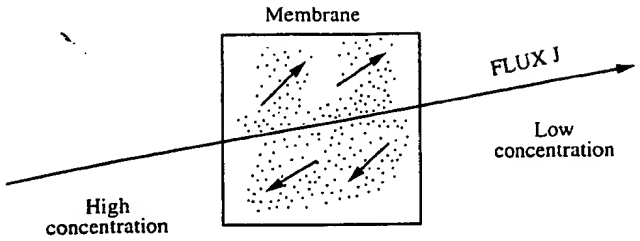

Fig. 3 Passive diffusion of molecules. Molecules in solution diffuse randomly in all directions. As molecules diffuse from left to right and vice versa (small arrows), a net diffusion from the high-concentration side to the low-concentration side results. This results in a net flux (J) to the right side. Flux is measured in mass per unit area (e.g., mg/cm^2). (From Ref. 1.)

of membrane; h = membrane thickness; and $C_{GI} - C_p$ = difference between the concentrations of drug in the GI tract and in the plasma.

Drug distributes rapidly into a large volume after entering the blood resulting in a very low plasma drug concentration with respect to the concentration at the site of drug administration. Drug is usually given in milligram doses, whereas plasma drug concentrations are often in the microgram per milliliter or nanogram per milliliter range. For drugs given orally, $C_{GI} \gg C_p$. A large concentration gradient is maintained driving drug molecules into the plasma from the GI tract.

As shown by Fick's Law of Diffusion, lipid solubility of the drug and the surface area and the thickness of the membrane influence the rate of passive diffusion of drugs. The partition coefficient, K, represents the lipid–water partitioning of a drug. More lipid soluble drugs have larger K values that theoretically increase the rate of systemic drug absorption. In practice, drug absorption is influenced by other physical factors of the drug, limiting its practical application of K. The surface area of the membrane through which the drug is absorbed directly influences the rate of drug absorption. Drugs may be absorbed from most areas of the GI tract. However, the duodenal area of the small intestine shows the most rapid drug absorption due to such anatomic features as villi and microvilli, which provide a large surface area. These villi are not found in such numbers in other areas of the GI tract.

The membrane thickness, h, is a constant at the absorption site but may be altered by disease. Drugs usually diffuse very rapidly into tissues through capillary cell membranes in the vascular compartments. In the brain, the capillaries are densely lined with glial cells creating a thicker lipid barrier (blood–brain barrier) causing a drug to diffuse more slowly into brain. In certain disease states (e.g., meningitis) the cell membranes may be disrupted or become more permeable to drug diffusion.

Many drugs have lipophilic and hydrophilic substituents. More lipid soluble drug molecules traverse cell membranes more easily than less lipid-soluble (i.e., more water-soluble) molecules. For weak electrolyte drugs (i.e, weak acids, bases), the extent of ionization influences drug solubility and the rate of drug transport. Ionized drugs are more water soluble than nonionized drugs which are more lipid soluble. The extent of ionization of a weak electrolyte depends on the pKa of the drug and the partition hypothesis (pH) of the medium in which the drug is dissolved. The Henderson and Hasselbalch equation describes the ratio of ionized (charged) to unionized form of the drug and is dependent on the pH conditions and the pKa of the drug:

For weak acids,

$$\text{Ratio} = -\frac{(\text{salt})}{(\text{acid})} = \frac{(A^-)}{(HA)} = 10^{(pH-pKa)}$$

For weak bases,

$$\text{Ratio} = -(\text{base})\,(\text{salt}) = (RNH)2\,(RNH^{+3}) = 10^{(pH-pKa)}$$

According to the pH, a weak acid (e.g., salicylic acid) should be rapidly absorbed from the stomach (pH 1.2) due to a favorable concentration gradient of the unionized (more lipid soluble) drug from the stomach to the blood, because practically all the drug in the blood compartment is dissociated (ionized) at pH 7.4. A weak base (e.g., quinidine) is highly ionized in acid pH and is poorly absorb from the stomach. Although many drugs obey by the pH, in practice, the major site of absorption of most drugs is usually in the small intestine (duodenum) due presence of a large surface area and high blood flow.

The drug concentration on either side of a membrane is also influenced by the affinity of the drug for a tissue component, which prevents the drug from freely moving back across the cell membrane. For example, drug that binds plasma or tissue proteins causes the drug to concentrate in that region. Dicumarol and sulfonamides strongly bind plasma proteins; whereas, chlordane, a lipid-soluble insecticide, partitions and concentrates into adipose (fat) tissue. Tetracycline forms a complex with calcium and concentrates in the bones and teeth. Drugs may concentrate in a tissue due to a specific uptake or active transport process. Such processes have been demonstrated for iodide in thyroid tissue, potassium in the intracellular water, and certain catecholamines in adrenergic storage sites.

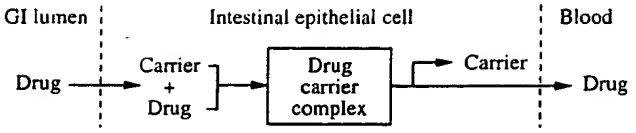

Fig. 4 Hypothetical carrier-mediated transport process. (From Ref. 1.)

Carrier-mediated transport

Theoretically, a lipophilic drug may pass through the cell or go around it. If drug has a low molecular weight and is lipophilic, the lipid cell membrane is not a barrier to drug diffusion and absorption. In the intestine, molecules smaller than 500 MW may be absorbed by paracellular drug absorption. Numerous specialized carrier-mediated transport systems are present in the body especially in the intestine for the absorption of ions and nutrients required by the body.

Active transport: Active transport is a carrier-mediated transmembrane process that is important for GI absorption of some drugs and also involved in the renal and biliary secretion of many drugs and metabolites. A carrier binds the drug to form a carrier–drug complex that shuttles the drug across the membrane and then dissociates the drug on the other side of the membrane (Fig. 4). Active transport is an energy-consuming system characterized by the transport of drug against a concentration gradient, that is, from regions of low drug concentrations to regions of high concentrations.

A drug may be actively transported, if the drug molecule structurally resembles a natural substrate that is actively transported. A few lipid-insoluble drugs that resemble natural physiologic metabolites (e.g., 5-fluorouracil) are absorbed from the GI tract by this process. Drugs of similar structure may compete for adsorption sites on the carrier. Because only a certain amount of carrier is available, the binding sites on the carrier may become saturated at high drug concentrations. In contrast, passive diffusion is not saturable.

Facilitated diffusion: Facilitated diffusion is a non-energy requiring, carrier-mediated transport system in which the drug moves along a concentration gradient (i.e., moves from a region of high drug concentration to a region of low drug concentration). Facilitated diffusion is saturable, structurally selective for the drug and shows competition kinetics for drugs of similar structure. Facilitated diffusion seems to play a very minor role in drug absorption.

Carrier-mediated intestinal transport: Various carrier mediated systems (transporters) are present at the intestinal brush border and basolateral membrane for the absorption of specific ions and nutrients essential for the body. Many drugs are absorbed by these carriers because of the structural similarity to natural substrates. An intestinal transmembrane protein, *P*-Glycoprotein (*P*-Gp) appears to reduce apparent intestinal epithelial cell permeability from lumen to blood for various lipophilic or cytotoxic drugs. Other transporters are present in the intestines. For example, many oral cephalosporins are absorbed through the amino acid transporter.

Vesicular transport

Vesicular transport is the process of engulfing particles or dissolved materials by the cell. Pinocytosis refers to the engulfment of small solutes or fluid, whereas phagocytosis refers to the engulfment of larger particles or macromolecules generally by macrophages. Endocytosis and exocytosis are the processes of moving macromolecules into and out of a cell, respectively.

During pinocytosis or phagocytosis, the cell membrane invaginates to surround the material, and then engulfs the material into the cell. Subsequently, the cell membrane containing the material forms a vesicle or vacuole within the cell. Vesicular transport is the proposed process for the absorption of orally administered sabin polio vaccine and various large proteins. An example of exocytosis is the transport of a protein such as insulin from insulin-producing cells of the pancreas into the extracellular space. The insulin molecules are first packaged into intracellular vesicles, which then fuse with the plasma membrane to release the insulin outside the cell.

ORAL DRUG ABSORPTION

Physiologic Considerations

Drugs may be administered by various routes of administration (Table 2). Except for intravenous drug administration, drugs are absorbed into the systemic circulation from the site of administration and are greatly affected by conditions at the administration site.

Oral administration is the most common route of drug administration. Major physiologic processes in the GI system include secretion, digestion, and absorption. Secretion includes the transport of fluid, electrolytes, peptides, and proteins into the lumen of the alimentary canal. Enzymes in saliva and pancreatic secretions are involved in the digestion of carbohydrates and proteins. Other secretions such as mucus protect the linings of the lumen of the GI tract. Digestion is the breakdown of food

constituents into smaller structures in preparation for absorption. Both drug and food constituents are mostly absorbed in the proximal area (duodenum) of the small intestinal. The process of absorption is the entry of constituents from the lumen of the gut into the body. Absorption may be considered as the net result of both lumen-to-blood and blood-to-lumen transport movements.

Drugs administered orally pass through various parts of the enteral canal including the oral cavity, esophagus, and various parts of the GI tract. Residues eventually exit the body through the anus. Drugs may be absorbed by passive diffusion from all parts of the alimentary canal including sublingual, buccal, GI, and rectal absorption. For most drugs, the optimum site for drug absorption after oral administration is the upper portion of the small intestine or duodenum region. The unique anatomy of the duodenum provides an immense surface area for the drug to passively diffuse (Table 4). In addition, the duodenal region is highly perfused with a network of capillaries, which helps to maintain a concentration gradient from the intestinal lumen and plasma circulation.

The total transit time, including gastric emptying, small intestinal transit, and colonic transit ranges from 0.4 to 5 days. Small intestine transit time (SITT) ranges from 3 to 4 h for most healthy subjects. If absorption is not completed by the time a drug leaves the small intestine, drug absorption may be erratic or incomplete. The small intestine is normally filled with digestive juices and liquids, keeping the lumen contents fluid. In contrast, the fluid in the colon is reabsorbed, and the lumen content in the colon is either semisolid or solid, making further drug dissolution erratic and difficult.

Gastrointestinal motility

Once the drug is given orally, the exact location and/or environment of the drug product within the GI tract is difficult to discern. GI motility tends to move the drug through the alimentary canal so that it may not stay at the absorption site. For drugs given orally, an anatomic absorption window may exist within the GI tract in which the drug is efficiently absorbed. Drugs contained in a nonbiodegradable controlled-release dosage form must be completely released into this absorption window prior to the movement of the dosage form into the large bowel. The transit time of the drug in the GI tract depends upon the pharmacologic properties of the drug, type of dosage form, and various physiologic factors. Physiologic movement of the drug within the GI tract depends upon whether the alimentary canal contains recently ingested food (digestive or fed state) or is in the fasted or interdigestive state.

Gastric emptying time

After oral administration, the swallowed drug rapidly reaches the stomach. Because the duodenum has the greatest capacity for the absorption of drugs from the GI tract, a delay in the gastric emptying time will slow the rate and possibly the extent of drug absorption from the duodenum, thereby prolonging the onset time for the drug. Drugs, such as penicillin, that are unstable in acid, may decompose if stomach emptying is delayed. Other drugs, (e.g., aspirin) may irritate the gastric mucosa during prolonged contact.

Factors that tend to delay gastric emptying include consumption of meals high in fat, cold beverages, and anticholinergic drugs. Liquids and small particles less than 1 mm are generally not retained in the stomach. These small particles are believed to be emptied due to a slightly higher basal pressure in the stomach over the duodenum. Different constituents of a meal will empty from the stomach at different rates. For example, liquids are generally emptied faster than digested solids from the stomach. Large particles, including tablets and capsules, are delayed from emptying for 3–6 h by the presence of food in the stomach. Indigestible solids empty very slowly, probably during the interdigestive phase, a phase in which food is not present and the stomach is less motile but periodically empties its content due to housekeeper wave contraction.

Intestinal motility

Normal peristaltic movements mix the contents of the duodenum, bringing the drug particles into intimate contact with the intestinal mucosal cells. The drug must have a sufficient time (residence time) at the absorption site for optimum absorption. In the case of high motility in the intestinal tract, as in diarrhea, the drug has a very brief residence time and less opportunity for adequate absorption.

Blood perfusion of the gastrointestinal tract

The blood flow is important in carrying the absorbed drug from the absorption site to the systemic circulation. A large network of capillaries and lymphatic vessels perfuse the duodenal region and peritoneum. The splanchnic circulation receives about 28% of the cardiac output and is increased after meals. Drugs are absorbed from the small intestine into the mesenteric vessels which flows to the hepatic-portal vein and then to the liver prior to reaching the systemic circulation. Any decrease in mesenteric blood flow, as in the case of congestive heart failure, will decrease the rate of systemic drug absorption from the intestinal tract.

Table 4 Drug absorption in the gastrointestinal tract

Anatomic area	Function	Affect on drug absorption
Oral cavity	Saliva, pH 7, contains ptyalin (salivary amylase), digests starches. Mucin, a glycoprotein, lubricates food and may interact with drugs.	Buccal and sublingual absorption occurs for lipid-soluble drugs.
Esophagus	The esophagus connects the pharynx and the cardiac orifice of the stomach. The pH is 5–6. The lower part of the esophagus ends with the esophageal sphincter, which prevents acid reflux from the stomach.	Tablets or capsules may lodge in this area, causing local irritation. Very little drug dissolution occurs in the esophagus.
Stomach	The fasting stomach pH is about 2 to 6. In the fed state, the stomach pH is about 1.5 to 2, due to hydrochloric acid secreted by parietal cells. Stomach acid secretion is stimulated by gastrin and histamine. Mixing is intense and pressurized in the antral part of the stomach, a process of breaking down large food particles described as antral milling. Food and liquid are emptied by opening the pyloric sphincter into the duodenum.	Drugs are not efficiently absorbed in the stomach. Basic drugs are solubilized rapidly in acid. Stomach emptying influences the time for drug reaching the small intestine. The food content and osmolality influenced by stomach emptying. Fatty acids delay gastric emptying. High-density foods generally are emptied more slowly from the stomach.
Duodenum	A common duct from the pancreas and gall bladder enters the duodenum. Duodenal pH is 6 to 6.5 due to the presence of bicarbonate that neutralizes the acidic chyme emptied from the stomach. The pH is optimum for enzymatic digestion of protein and peptide food. Pancreatic juice containing enzymes is secreted into the duodenum from the bile duct. Trypsin, chymotrypsin, and carboxypeptidase are involved in the hydrolysis of proteins into amino acids. Amylase is involved in the digestion of carbohydrates. Pancreatic lipase secretion hydrolyzes fats into fatty acids.	The main site for drug absorption. An immense surface area for the passive diffusion of drug to due to the presence of villi and microvilli forming a brush border. A high blood perfusion maintains a drug concentration gradient from the intestinal lumen and plasma circulation. The complex fluid medium in the duodenum dissolves many drugs with limited aqueous solubility. Ester prodrugs are hydrolyzed during absorption. Proteolytic enzymes degrade many protein drugs in the duodenum, preventing adequate absorption. Acid drugs dissolve in the alkaline pH. Bile secretion helps to dissolve fats and hydrophobic drugs
Jejunum	The jejunum is the middle portion of the small intestine in between the duodenum and the ileum. Digestion of protein and carbohydrates continues after receiving pancreatic juice and bile in the duodenum, this portion of the small intestine generally has less contraction than the duodenum and is preferred for in vivo drug absorption studies.	Drugs generally absorbed by passive diffusion.
Ileum	The ileum, pH about 7, with the distal part as high as 8, is the terminal part of the small intestine and has fewer contractions than the duodenum. The ileocecal valve separates the small intestine with the colon.	Drugs generally absorbed by passive diffusion.
Colon	The colon, pH 5.5–7, is lined with mucin functioning as lubricant and protectant. The colon contains both aerobic and anaerobic micro-organisms that may metabolize some drugs. Crohn's disease affects the colon and thickens the bowel wall. The microflora may also become more anaerobic. Absorption of clindamycin and propranolol are increased, whereas other drugs have reduced absorption with this disease (Rubinstein et al. 1988).	Very limited drug absorption due to the lack of microvilli and the more viscous and semisolid nature of the lumen contents. A few drugs such as theophylline and metoprolol are absorbed in this region. Drugs that are absorbed well in this region are good candidates for an oral sustained-release dosage form.

(*Continued*)

Table 4 Drug absorption in the gastrointestinal tract (*Continued*)

Anatomic area	Function	Affect on drug absorption
Rectum	The rectum is about 15 cm long, ending at the anus. In the absence of fecal material, the rectum has a small amount of fluid, (about 2 m) with a pH about 7. The rectum is perfused by the superior, middle, and inferior hemorrhoidal veins. The inferior hemorrhoidal vein (closest to the anal sphincter) and the middle hemorrhoidal vein feed into the vena cava and back to the heart. The superior hemorrhoidal vein joins the mesenteric circulation, which feeds into the hepatic portal vein and then to the liver.	Drug absorption may be variable depending upon the placement of the suppository or drug solution within the rectum. A portion of the drug dose may be absorbed via the lower hemorrhoidal veins, from which the drug feeds directly into the systemic circulation; some drug may be absorbed via the superior hemorrhoidal veins, which feeds into the mesenteric veins to the hepatic portal vein to the liver, and metabolized prior to systemic absorption.

Some drugs may be absorbed into the lymphatic circulation through the lacteal or lymphatic vessels under the microvilli. Absorption of drugs through the lymphatic system bypasses the first-pass effect due to liver metabolism, because drug absorption through the hepatic portal vein is avoided. The lymphatics are important in the absorption of dietary lipids and may be partially responsible for the absorption for some lipophilic drugs such as bleomycin or aclarubicin which may dissolve in chylomicrons and be systemically absorbed via the lymphatic system.

Effect of food and other factors on GI drug absorption

Digested foods may affect intestinal pH and solubility of drugs. Food effects are not always predictable. The absorption of some antibiotics (e.g., penicillin, tetracycline) is decreased with food, whereas other drugs (e.g., griseofulvin) are better absorbed when given with food containing a high fat content. Food in the GI lumen stimulates the flow of bile. Bile contains bile acids. Bile acids are surfactants are involved in the digestion and solubilization of fats, and increases the solubility of fat-soluble drugs through micelle formation. For some basic drugs (e.g., cinnarizine) with limited aqueous solubility, the presence of food in the stomach stimulates hydrochloric acid secretion, which lowers the pH, causing more rapid dissolution of the drug and better absorption.

Generally, the bioavailability of drugs is better in patients in the fasted state and with a large volume of water (Fig. 5). However, to reduce GI mucosal irritation, drugs such as erythromycin, iron salts, aspirin, and nonsteroidal anti-inflammatory agents (NSAIDs) are given with food. The rate of absorption for these drugs may be reduced in the presence of food, but the extent of absorption may be the same.

The drug dosage form may also be affected by food. For example, enteric-coated tablets may stay in the stomach for a longer period of time because food delays stomach emptying. If the enteric-coated tablet does not reach the duodenum rapidly, drug release and subsequent systemic drug absorption are delayed. In contrast, enteric-coated beads or microparticles disperse in the stomach, are less affected by food, and demonstrate more consistent drug absorption from the duodenum.

Food may also affect the integrity of the dosage form, causing an alteration in the release rate of the drug. For example, theophylline bioavailability from Theo-24 controlled-release tablets is much more rapid (7) when given to a subject in the fed rather than fasted state (Fig. 6).

Some drugs, such as ranitidine, cimetidine, and dipyridamole, after oral administration produce a blood concentration curve consisting of two peaks. This double-peak phenomenon is generally observed after the administration of a single dose to fasted patients. The rationale for the double-peak phenomenon has been attributed to variability in stomach emptying, variable intestinal motility, presence of food, enterohepatic recycling, or failure of a tablet dosage form. For a drug with high water solubility, dissolution of the drug occurs in the stomach, and partial emptying of the drug into the duodenum will result in the first absorption peak. A delay in stomach emptying results in a second absorption peak as the remainder of the dose is emptied into the duodenum.

Diseases such as Crohn's disease that alter GI physiology and corrective surgery involving peptic ulcer, antrectomy with gastroduodenostomy and selective vagotomy may potentially affect drug absorption. Drug absorption may be unpredictable in many disease conditions. Drugs or nutrients or both may also affect the absorption of other drugs. For example, propantheline

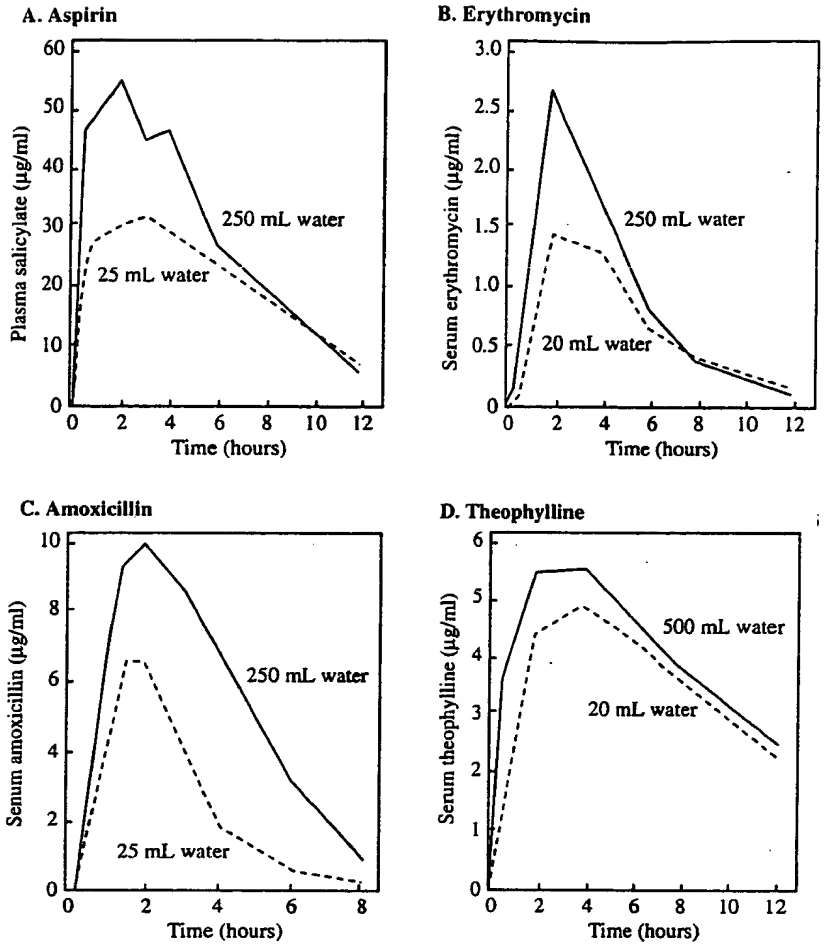

Fig. 5 Mean plasma or serum drug levels in healthy, fasting human volunteers ($n = 6$ in each case) who received single oral doses of aspirin (650 mg) tablets, erythromycin stearate (500 mg) tablets, amoxicillin (500 mg) capsules, and theophylline (260 mg) tablets, together with large. (From Welling P.G.; Drug Bioavailability and Its Clinical Significance. *Progress in Drug Metabolism*, Vol. 4; Bridges K.W.; Chassea, VD LF. Eds.; Wiley; London, 1980.)

bromide is an anticholinergic drug that slows stomach emptying and motility of the small intestine and may reduce stomach acid secretion. Grapefruit juice was found to increase the plasma level of many drugs due to inhibition of their metabolism in the liver.

PHARMACEUTICAL FACTORS AFFECTING DRUG BIOAVAILABILITY

Biopharmaceutic considerations in the design and manufacture of a drug product to deliver the active drug with the desired bioavailability characteristics include: 1) the type of drug product (e.g., solution, suspension, suppository), 2) the nature of the excipients in the drug product, 3) the physicochemical properties of the drug molecule, and 4) the route of drug administration.

Disintegration

Immediate release, solid oral drug products must rapidly disintegrate into small particles and release the drug. The United States Pharmacopoeia (USP) describes an official tablet disintegration test. The process of disintegration does not imply complete dissolution of the tablet and/or the drug. Complete disintegration is defined by the USP as "that state in which any residue of the tablet, except fragments of insoluble coating, remaining on the screen of

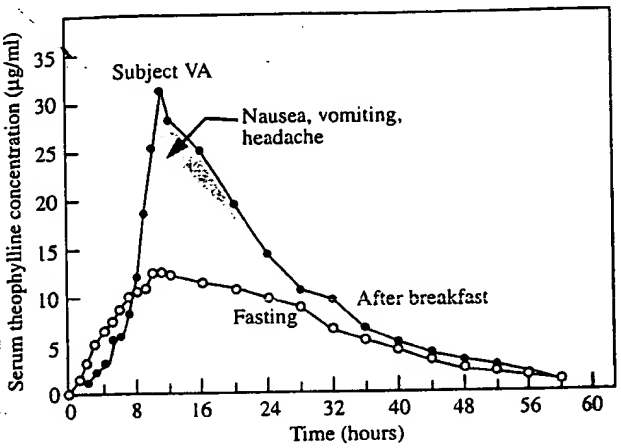

Fig. 6 Theophylline serum concentration in an individual subject after a single 1500 mg dose of Theo-24 taken during fasting, period during which this patient experienced nausea, repeated vomiting, or severe throbbing headache. The pattern of drug release during the food regimen is consistent with "dose-dumping." (From Ref. 7.)

the test apparatus in the soft mass have no palpably firm core." The USP provides specifications for uncoated tablets, plain coated tablets, enteric tablets, buccal tablets, and sublingual tablets. Exempted from USP disintegration tests are troches, tablets which are intended to be chewed, and drug products intended for sustained release or prolonged or repeat action.

Disintegration tests allow for precise measurement of the formation of fragments, granules, or aggregates from solid dosage forms, but do not provide information on the dissolution rate of the active drug. The disintegration test serves as a component in the overall quality control of tablet manufacture.

Dissolution

Dissolution is the process by which a chemical or drug becomes dissolved in a solvent. In biologic systems, drug dissolution in an aqueous medium is an important prior condition of systemic absorption. The rate at which drugs with poor aqueous solubility dissolve from an intact or disintegrated solid dosage form in the GI tract often controls the rate of systemic absorption of the drug. Thus, dissolution tests are discriminating of formulation factors that may affect drug bioavailability.

As the drug particle dissolves, a saturated solution (stagnant layer) is formed at the immediate surface around the particle. The dissolved drug in the saturated solution gradually diffuses to the surrounding regions. The overall rate of drug dissolution may be described by the Noyes–Whitney equation which models drug dissolution in terms of the rate of drug diffusion from the surface to the bulk of the solution. In general, drug concentration at the surface is assumed to be the highest possible, i.e., the solubility of the drug in the dissolution medium. The drug concentration C is the homogeneous concentration in the bulk solution which is generally lower than that in the stagnant layer immediate to the surface of the solid. The decrease in concentration across the stagnant layer is called the diffusion gradient

$$dC/dt = DA(CS - C)h$$

where, dC/dt = rate of drug dissolution, D = diffusion rate constant, A = surface area of the particle, CS = drug concentration in the stagnant layer, C = drug concentration in the bulk solvent, and h = thickness of the stagnant layer.

The rate of dissolution, $(dC/dt) \times (1/A)$, is the amount of drug dissolved per unit area per time (e.g., g/cm^2 per min).

The Noyes–Whitney equation shows that dissolution rate is influenced by the physicochemical characteristics of the drug, the formulation, and the solvent. In addition, the temperature of the medium also affects drug solubility and dissolution rate.

PHYSICOCHEMICAL NATURE OF THE DRUG

Solubility, pH, and Drug Absorption

The natural pH environment of the GI tract varies from acidic in the stomach to slightly alkaline in the small intestine. Drug solubility may be improved with the addition of acidic or basic excipients. Solubilization of aspirin, for example, may be increased by the addition of an alkaline buffer. Controlled release drug products are nondisintegrating dosage forms. Buffering agents may be added to slow or modify the release rate of a fast-dissolving drug in the formulation of a controlled release drug product. The buffering agent is released slowly rather than rapidly so that the drug does not dissolve immediately in the surrounding GI fluid. Intravenous drug solutions are difficult to prepare with drugs that have poor aqueous solubility. Drugs that are physically or chemically unstable may require special excipients, coating or manufacturing process to protect the drug from degradation.

Stability, pH, and Drug Absorption

The pH-stability profile is a plot of reaction rate constant for drug degradation versus pH and may help to predict if

some of the drug will decompose in the GI tract. The stability of erythromycin is pH-dependent. In acidic medium, erythromycin decomposition occurs rapidly, whereas at neutral or alkaline pH the drug is relatively stable. Consequently, erythromycin tablets are enteric coated to protect against acid degradation in the stomach. In addition, less soluble erythromycin salts that are more stable in the stomach have been prepared.

Particle Size and Drug Absorption

The effective surface area of the drug is increased enormously by a reduction in the particle size. Because drug dissolution is thought to take place at the surface of the solute, the greater the surface area, the more rapid the rate of drug dissolution. The geometric shape of the drug particle also affects the surface area, and during dissolution the surface is constantly changing. In dissolution calculations, the solute particle is usually assumed to have retained its geometric shape.

Particle size and particle size distribution studies are important for drugs that have low water solubility. Particle size reduction by milling to a micronized form increased the absorption of low aqueous solubility drugs such as griseofulvin, nitrofurantoin, and many steroids. Smaller particle size results in an increase in the total surface area of the particles, enhances water penetration into the particles, and increases the dissolution rates. With poorly soluble drugs, a disintegrant may be added to the formulation to ensure rapid disintegration of the tablet and release of the particles.

Polymorphic Crystals, Solvates, and Drug Absorption

Polymorphism refers to the arrangement of a drug in various crystal forms (polymorphs). Polymorphs have the same chemical structure but different physical properties, such as solubility, density, hardness, and compression characteristics. Some polymorphic crystals may have much lower aqueous solubility than the amorphous forms, causing a product to be incompletely absorbed. Chloramphenicol (9), for example, has several crystal forms, and when given orally as a suspension, the drug concentration in the body depended on the percentage of β-Polymorph in the suspension. The β-form is more soluble and better absorbed (Fig. 7). In general, the crystal form that has the lowest free energy is the most stable polymorph. Polymorphs that are metastable may convert to a more stable form over time. A crystal form change may cause problems in manufacturing the product. For example, a

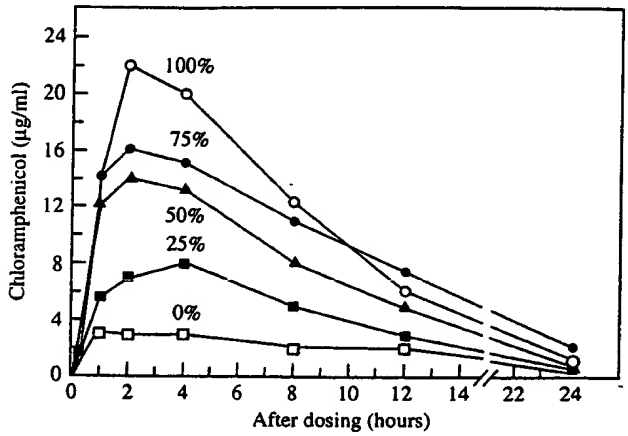

Fig. 7 Comparison of mean blood serum levels obtained with chloramphenicol palmitate suspensions containing varying ratios of α and β polymorphs, following single oral dose equivalent. (From Ref. 9.)

change in crystal structure of the drug may cause cracking in a tablet or even prevent a granulation to be compressed into a tablet requiring reformulation of the product. Some drugs interact with solvent during preparation to form a crystal called solvate. Water may form a special crystal with drugs called hydrates, for example, erythromycin forms different hydrates (8) which may have quite different solubility compared to the anhydrous form of the drug (Fig. 8). Ampicillin trihydrate, for example, was reported

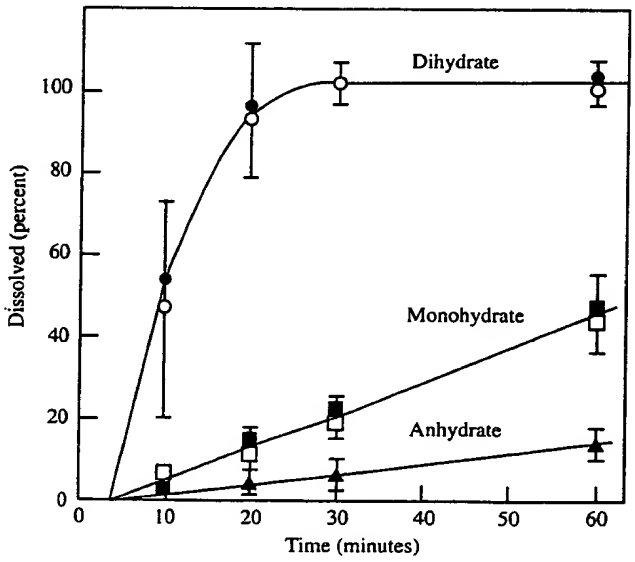

Fig. 8 Dissolution behavior of erythromycin dihydrate, monohydrate, and anhydrate in phosphate buffer (pH 7.5) at 37°C. (From Ref. 8.)

Table 5 Common excipients used in solid drug products

Excipient	Property in dosage form
Lactose	Diluent
Dibasic calcium phosphate	Diluent
Starch	Disintegrant, diluent
Microcrystalline cellulose	Disintegrant, diluent
Magnesium stearate	Lubricant
Stearic acid	Lubricant
Hydrogenated vegetable oil	Lubricant
Talc	Lubricant
Sucrose (solution)	Granulating agent
Polyvinyl pyrrolidone (solution)	Granulating agent
Hydroxypropylmethylcellulose	Tablet-coating agent
Titinium dioxide	Combined with dye as colored coating
Methylcellulose	Coating or granulating agent
Cellulose acetate phthalate	Enteric coating agent

(From Ref. 1.)

Table 6 Common excipients used in oral liquid drug products

Excipient	Property in dosage form
Sodium carboxymethylcellulose	Suspending agent
Tragacanth	Suspending agent
Sodium alginate	Suspending agent
Xanthan gum	Thixotropic suspending agent
Veegum	Thixotropic suspending agent
Sorbitol	Sweetener
Alcohol	Solubilizing agent, preservative
Propylene glycol	Solubilizing agent
Methyl propylparaben	Preservative
Sucrose	Sweetener
Polysorbates	Surfactant
Sesame oil	For emulsion vehicle
Corn oil	For emulsion vehicle

(From Ref. 1.)

to be less absorbed than the anhydrous form of ampicillin due to faster dissolution of the latter.

FORMULATION FACTORS AFFECTING DRUG DISSOLUTION

Excipients are pharmacodynamically inactive substances that are added to a formulation to provide certain functional properties to the drug and dosage form. Excipients may be added to improve the compressibility of the active drug, stabilize the drug from degradation, decrease gastric irritation, control the rate of drug absorption from the absorption site, increase drug bioavailability, etc. Some excipients used in the manufacture of solid and liquid drug products are listed in Tables 5 and 6. For solid oral dosage forms such as compressed tablets, excipients may include 1) diluent (e.g., lactose), 2) disintegrant (e.g., starch), 3) lubricant (e.g., magnesium stearate), and 4) other components such as binding and stabilizing agents. When improperly used in the formulation, excipients may alter drug bioavailability and possibly pharmacodynamic activity.

Excipients may affect the drug dissolution rate by altering the medium in which the drug is dissolving or by reacting with the drug itself. Some common manufacturing problems that affect drug dissolution and bioavailability are listed in Table 7. For example,

Table 7 Effect of excipients on the pharmacokinetic parameters of oral drug product[a]

Excipients	Example	k_a	t_{max}	AUC
Disintegrants	Avicel, Explotab	↑	←	↑/—
Lubricants	Talc, hydrogenated vegetable oil	←	↑	←/—
Coating agent	Hydroxypropylmethyl cellulose	—	—	—
Enteric coat	Cellulose acetate phthalate	←	↑	←/—
Sustained-release agents	Methylcellulose, ethylcellulose	←	↑	←/—
Sustained-release agents (waxy agents)	Castorwax, Carbowax	←	↑	←/—
Sustained-release agents (gum/viscous)	Veegum, Keltrol	←	↑	←/—

[a]This may be concentration and drug dependent.
↑ = Increase, ← = decrease, — = no effect. k_a = absorption rate constant, t_{max} = time for peak drug concentration in plasma, AUC = area under the plasma drug concentration time curve.
(From Ref. 1.)

suspending agents increase the viscosity of the drug vehicle, but may decrease the drug dissolution rate from the suspension. An excessive quantity of magnesium stearate (a hydrophobic lubricant) in the formulation may retard drug dissolution and slow the rate of drug absorption. The total amount of drug absorbed may also be reduced. To prevent this problem, the lubricant level should be decreased or a different lubricant selected. Sometimes, increasing the amount of disintegrant may overcome the retarding effect of lubricants on dissolution. However, with some poorly soluble drugs an increase in disintegrant level has little or no effect on drug dissolution because the fine drug particles are not wetted. The general influence of some common excipients on drug bioavailability parameters for typical oral drug products is summarized in Table 7.

Excipients may enhance or diminish the rate and extent of systemic drug absorption. Excipients that increase the aqueous solubility of the drug generally increase the rate of drug dissolution and absorption. For example, sodium bicarbonate in the formulation may change the pH of the medium surrounding the active drug substance. Aspirin, a weak acid, in an alkaline medium will form a water-soluble salt in which the drug rapidly dissolves. This process is known as dissolution in a reactive medium. The solid drug dissolves rapidly in the reactive solvent surrounding the solid particle. As the dissolved drug molecules diffuse outward into the bulk solvent, the drug may precipitate out of solution with a very fine particle size. The small particles have enormous collective surface area and disperse and redissolve readily for more rapid absorption on contact with the mucosal surface.

Excipients may interact directly with the drug to form a water-soluble or water-insoluble complex. If tetracycline is formulated with calcium carbonate, an insoluble complex of calcium tetracycline is formed that has a slow rate of dissolution and poor absorption.

Excipients may increase the retention time of the drug in the GI tract and therefore increase the amount of drug absorbed. Excipients may act as carriers to increase drug diffusion across the intestinal wall. The addition of surface-active agents may increase wetting as well as solubility of drugs. In contrast, many excipients may retard drug dissolution and thus reduce drug absorption.

Shellac used as a tablet coating, upon aging, can slow the drug dissolution rate. Surfactants may affect drug dissolution in an unpredictable fashion. Low concentrations of surfactants lower the surface tension and increase the rate of drug dissolution, whereas higher concentrations of surfactants tend to form micelles with the drug and thus decrease the dissolution rate. High tablet compression without sufficient disintegrant may cause poor disintegration in vivo of a compressed tablet.

IN VITRO DISSOLUTION TESTING

A dissolution test in vitro measures the rate and extent of dissolution of the drug in an aqueous medium in the presence of one or more excipients contained in the drug product. A potential bioavailability problem may be uncovered by a suitable dissolution method. The optimum dissolution testing conditions differ with each drug formulation. Different agitation rates, different medium (including different pH), and different dissolution apparatus should be tried to distinguish which dissolution method is optimum for the drug product and discriminating for drug formulation changes. The appropriate dissolution test condition for the drug product is then used to determine acceptable dissolution specifications.

The size and shape of the dissolution vessel may affect the rate and extent of dissolution. For example, the vessel may range in size from several milliliters to several liters. The shape may be round-bottomed or flat, so that the tablet might lie in a different position in different experiments. The amount of agitation and the nature of the stirrer affect the dissolution rate. Stirring rates must be controlled, and specifications differ between drug products. Low stirring rates (50–100 rpm) are more discriminating of formulation factors affecting dissolution than higher stirring rates. The temperature of the dissolution medium must be controlled and variations in temperature must be avoided. Most dissolution tests are performed at 37°C.

The nature of the dissolution medium, the solubility of the drug and the amount of drug in the dosage form will affect the dissolution test. The dissolution medium should not be saturated by the drug. Usually, a volume of medium larger than the amount of solvent needed to completely dissolve the drug is used in such tests. The usual volume of the medium is 500–1000 ml. Drugs that are not very water soluble may require use of a very-large-capacity vessel (up to 2000 ml) to observe significant dissolution. Sink conditions is a term referring to an excess volume of medium that allows the solid drug to continuously dissolve. If the drug solution becomes saturated, no further net drug dissolution will take place. According to the USP, "the quantity of medium used should be not less than three times that required to form a saturated solution of the drug substance."

Which medium is best is a matter of considerable controversy. The preferred dissolution medium in USP dissolution tests is deaerated water or if substantiated by the solubility characteristics of the drug or formulation, a buffered aqueous solution (typically pH 4–8) or dilute HCl may be used. The significance of dearation of the medium should be determined. Various investigators have used 0.1 *N* HCl, 0.01 *N* HCl, phosphate buffer, simulated gastric juice, water, and simulated intestinal juice, depending on the nature of the drug product and the location in the GI tract where the drug is expected to dissolve. No single apparatus and test can be used for all drug products. Each drug product must be tested individually with the dissolution test that best correlates to in vivo bioavailability.

The dissolution test usually states that a certain percentage of the labeled amount of drug in the drug product must dissolve within a specified period of time. In practice, the absolute amount of drug in the drug product may vary from tablet to tablet. Therefore, a number of tablets from each lot are usually tested to get a representative dissolution rate for the product. The USP provides several official (compendia) methods for carrying out dissolution tests of tablets, capsules and other special products such as transdermal preparations. The selection of a particular method for a drug is usually specified in the monograph for a particular drug product.

BIOAVAILABILITY AND BIOEQUIVALENCE

Bioavailability and bioequivalence may be determined directly using plasma drug concentration vs. time profiles, urinary drug excretion studies, measurements of an acute pharmacologic effect, clinical studies, or in vitro studies. Bioavailability studies are performed for both approved active drug ingredients or therapeutic moieties not yet approved for marketing by the FDA. New formulations of active drug ingredients or therapeutic moieties must be approved, prior to marketing, by the FDA. In approving a drug product for marketing, the FDA must ensure that the drug product is safe and effective for its labeled indications for use. To ensure that the drug product meets all applicable standards of identity, strength, quality, and purity, the FDA requires bioavailability/pharmacokinetic studies and where necessary bioequivalence studies for all drug products.

For unmarketed drugs which do not have full New Drug Application (NDA) approval by the FDA, in vivo bioavailability studies must be performed on the drug formulation proposed for marketing. Essential pharmacokinetic parameters of the active drug ingredient or therapeutic moiety is also characterized. Essential pharmacokinetic parameters include the rate and extent of systemic absorption, elimination half-life, and rates of excretion and metabolism should be established after single- and multiple-dose administration. Data from these in vivo bioavailability studies are important to establish recommended dosage regimens and to support drug labeling.

In vivo bioavailability studies are performed also for new formulations of active drug ingredients or therapeutic moieties that have full NDA approval and are approved for marketing. The purpose of these studies is to determine the bioavailability and characterize the pharmacokinetics of the new formulation, new dosage form, or new salt or ester relative to a reference formulation. After the bioavailability and essential pharmacokinetic parameters of the active ingredient or therapeutic moiety are established, dosage regimens may be recommended in support of drug labeling.

Bioequivalent Drug Products

Bioequivalent drug products are pharmaceutical equivalents whose bioavailability (i.e., rate and extent of systemic drug absorption) does not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single or multiple dose. Some pharmaceutical equivalents or may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered medically insignificant for the particular drug product studied [21 CFR 320.1(e)].

Generic Drug Products

A generic drug product is considered bioequivalent to the reference listed drug product (generally the currently marketed, brand-name product with a full (NDA) approved by the FDA) if both products are pharmaceutical equivalents and its rate and extent of systemic drug absorption (bioavailability) do not show a statistically significant difference when administered in the same dose of the active ingredient, in the same chemical form, in a similar dosage form, by the same route of administration, and under the same experimental conditions.

Pharmaceutical equivalents are drug products that contain the same therapeutically active drug ingredient(s), same salt, ester, or chemical form; are of the same dosage form; and are identical in strength and concentration and route of administration. Pharmaceutical equivalents may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, and excipients (including colors, flavoring, preservatives).

Therapeutic equivalent drug products are pharmaceutical equivalents that can be expected to have the same clinical effect and safety profile when administered to patients under the same conditions specified in the labeling. Therapeutic equivalent drug products have the following criteria: 1) The products are safe and effective; 2) The products are pharmaceutical equivalents containing the same active drug ingredient in the same dosage form, given by the same route of administration, meet compendia or other applicable standards of strength, quality, purity, and identity and meet an acceptable in vitro standard; 3) The drug products are bioequivalent in that they do not present a known potential problem and are shown to meet an appropriate bioequivalence standard; 4) The drug products are adequately labeled; 5) The drug products are manufactured in compliance with current good manufacturing practice (GMP) regulations.

The generic drug product requires an abbreviated new drug application (ANDA) for approval by the FDA and may be marketed after patent expiration of the reference listed drug product. The generic drug product must be a therapeutic equivalent to the Reference drug product but may differ in certain characteristics including shape, scoring configuration, packaging, and excipients (includes colors, flavors, preservatives, expiration date, and minor aspects of labeling).

Pharmaceutical alternatives are drug products that contain same therapeutic moiety but are different salts, esters or complexes (e.g., tetracycline. hydrochloride versus tetracycline phosphate) or are different dosage forms (e.g., tablet versus capsule; immediate release dosage form versus controlled release dosage form) or strengths.

In summary, clinical studies are useful in determining the safety and efficacy of the drug product. Bioavailability studies are used to define the affect of changes in the physico chemical properties of the drug substance and the affect of the drug product (dosage form) on the pharmacokinetics of the drug; whereas, bioequivalence studies are used to compare the bioavailability of the same drug (same salt or ester) from various drug products. If the drug products are bioequivalent and therapeutically equivalent, then the clinical efficacy and safety profile of these drug products are assumed to be similar and may be substituted for each other.

DRUG PRODUCT PERFORMANCE IN VITRO AS A MEASURE OF IN VIVO DRUG BIOAVAILABILITY

The best measure of a drug product's performance is to give the drug product to human volunteers or patients and then determine the in vivo bioavailability of the drug using a pharmacokinetic or clinical study. For some well characterized drug products and for certain drug products where bioavailability is self-evident (e.g., sterile solutions for injection), in vivo bioavailability studies may be unnecessary. In these cases, the performance of the drug product in vitro is used as a surrogate to predict the in vivo drug bioavailability. Because these products have predictable in vivo performance as judged by the in vitro characterization of the drug and drug product, the FDA may waive the requirement for performing an in vivo bioavailability study (Table 8).

Drug Products for which Bioavailability is Self-Evident

Drug bioavailability from a true solution is generally considered self-evident. Thus, sterile solutions, lyophilized powders for reconstitution, opthalmic solutions do not need bioequivalence studies but still must be manufactured according to current GMPs. However, highly viscous solutions may have bioavailability problems due to slow diffusion of the active drug.

In Vitro–In Vivo Correlation (IVIVC)

In vitro bioavailability data may be used to predict the performance of a dosage provided that the dissolution method selected is appropriate for the solid oral dosage form and prior information has been collected showing that the dissolution method will result in optimum drug absorption from the drug product. In general, IVIVC is best for well absorbed drugs for which the dissolution rate is the rate-limiting step. Some drugs are poorly absorbed and dissolution is not predictive of absorption (1). The objectives of IVIVC are to use rate of dissolution as a discriminating (i.e., sensitive to changes in formulation or manufacturing process), as an aid in setting dissolution specifications. When properly applied, IVIVC may be used to facilitate the evaluation

Table 8 Examples of drug products for which in vivo bioavailability studies may be waived

Condition	Example	Comment
Drug products for which bioavailability is self-evident	Drug solution (e.g., parenteral ophthalmic, oral solutions)	Drug bioavailability from a true solution is considered self-evident. However, highly viscous solutions may have bioavailability problems.
In vivo–in vitro correlation (IVIVC)	Modified release drug products	The dissolution of the drug from the drug product in vitro must be highly correlated to the in vivo bioavailability of the drug.
Biopharmaceutic classification (BCS) system	Immediate release solid oral drug products	Drug must be a highly soluble and highly permeable substance that is in a rapidly dissolving dosage form.
Biowaiver	Drug product containing a lower dose strength	Drug product is in the same dosage form, but lower strength and is proportionally similar in its active and inactive ingredients.

of drug products with manufacturing changes including minor changes in formulation, equipment, process, manufacturing site, and batch size. (see section on SUPAC) (2, 3, 10).

Three levels of IVIVC are generally recognized by the FDA (10). Level A correlation is usually estimated by deconvolution followed by comparison of the fraction of drug absorbed to the fraction of drug dissolved. A correlation of this type is the highest level of correlation and best predictor of bioavailability from the dosage form. A Level A correlation is generally linear and represents a point-to-point relationship between in vitro dissolution rate and the in vivo input rate. The Level A correlation should predict the entire in vivo time course from the in vitro dissolution data. Level B correlation utilizes the principles of statistical moment analysis, Various dissolution IVIVC methods were discussed by Shargel and Yu in 1985, 1993, 1999 (1). The mean in vitro dissolution time is compared to either the mean residence time or the mean in vivo dissolution time. Level B correlation, like Level A correlation, uses all of the in vitro and in vivo data but is not considered to be a point-to-point correlation and does not uniquely reflect the actual in vivo plasma level curve, since several different in vivo plasma level-time curves will produce similar residence times. A Level C correlation is the weakest IVIVC and establishes a single point relationship between a dissolution parameter (e.g., time for 50% of drug to dissolve, or percent drug dissolved in two hours, etc.) and a pharmacokinetic parameter (e.g., AUC, Cmax, Tmax). Level C correlation does not reflect the complete shape of the plasma drug concentration-time curve of dissolution profile.

BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

The FDA may waive the requirement for performing an in vivo bioavailability or bioequivalence study for certain immediate release solid oral drug products that meets very specific criteria, namely, the permeability, solubility, and dissolution of the drug. These characteristics include the in vitro dissolution of the drug product in various media, drug permeability information, and assuming ideal behavior of the drug product, drug dissolution and absorption in the GI tract. For regulatory purpose, drugs are classified according to BCS in accordance the solubility, permeability and dissolution characteristics of the drug (FDA Draft Guidance for Industry, January, 1999, see FDA website for guidance) (11). Based on drug solubility and permeability, Amidon et al. (10, 12) recommended the following BCS in 1995 (Table 9).

This classification can be used as a basis for setting in vitro dissolution specifications and can also provide a basis for predicting the likelihood of achieving a successful in IVIVC. The solubility of a drug is determined by dissolving the highest unit dose of the drug in 250 ml of buffer adjusted between pH 1.0 and 8.0. A drug substance is considered highly soluble when the dose/solubility volume of solution are less than or equal to 250 ml. High-permeability drugs are generally those with an extent of absorption that is greater than 90%.

Solubility

An objective of the BCS approach is to determine the equilibrium solubility of a drug under approximate

Table 9 Biopharmaceutics classification system (BCS)

Condition	Comments
Solubility	A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of water over a pH range of 1–8.
Dissolution	An immediate release (IR) drug product is considered rapidly dissolving when not less than 85% of the label amount of the drug substance dissolves within 30 min using the USP apparatus I at 100 rpm (or apparatus II at 50 rpm) in a volume of 900 ml or less.[a]
Permeability	A drug substance is considered highly permeable when the extent of absorption in humans is to be >90% of an administered dose based on mass balance determination.

[a]Media include: acidic media (e.g., 0.1 N HCl) or simulated gastric fluid, USP without enzymes, pH 4.5 buffer and pH 6.8 buffer of simulated intestinal fluid, USP without enzymes (From FDA Draft Guidance, Jan, 1999.)

physiological conditions. For this purpose, determination of pH-solubility profiles over a pH range of 1–8 is suggested. Preferably eight or more pH conditions should be evaluated. Buffers that react with the drug should not be used. An acid or base titration method can also be used for determining drug solubility. The solubility class is determined by calculating what volume of an aqueous media is sufficient to dissolve the highest anticipated dose strength. A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1–8. The volume estimate of 250 ml is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (8 ounces) of water.

Solution stability of a test drug in selected buffers (or pH conditions) should be documented using a validated stability-indicating assay. Data collected on both pH-solubility and pH-stability should be submitted in the biowaiver application along with information on the ionization characteristics, such as pKa(s), of a drug.

Determining Permeability Class

Studies of the extent of absorption in humans, or intestinal permeability methods, can be used to determine the permeability class membership of a drug. To be classified as highly permeable, a test drug should have an extent of absorption >90% in humans. Supportive information on permeability characteristics of the drug substance should also be derived from its physical–chemical properties (e.g., octanol:water partition coefficient).

Some methods to determine the permeability of a drug from the GI tract include 1) in vivo intestinal perfusion studies in humans, 2) in vivo or in situ intestinal perfusion studies in animals, 3) in vitro permeation experiments using excised human or animal intestinal tissues, and 4) in vitro permeation experiments across a monolayer of cultured human intestinal cells. When using these methods, the experimental permeability data should correlate with the known extent-of-absorption data in humans.

Table 10 Postapproval change levels

Change level	Example	Comment
Level 1	Deletion or partial deletion of an ingredient to affect the color or flavor of the drug product	Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.
Level 2	Quantitative change in excipients greater that allowed in a Level 1 change.	Level 2 changes are those that could have a significant impact on formulation quality and performance
Level 3	Qualitative change in excipients	Level 3 changes are those that are likely to have a significant impact on formulation quality and performance. A Level 3 change may require in vivo bioequivalence testing.

Dissolution

The dissolution class is based on the in vitro dissolution rate of an immediate release drug product under specified test conditions and is intenended to indicate rapid in vivo dissolution in relation to the average rate of gastric emptying in humans under fasting conditions. An immediate release drug product is considered rapidly dissolving when not less than 85% of the label amount of drug substance dissolves within 30 min using the USP apparatus I at 100 rpm or apparatus II at 50 rpm in a voluume of 900 ml or less in each of the following media 1) acidic media such as 0.1 *N* HCl or Simulated Gastric Fluid USP without enzymes; 2) a pH 4.5 buffer; and 3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

BIOWAIVERS

In addition to routine quality control tests, comparative dissolution tests have been used to waive bioequivalence requirements (biowaivers) for lower strengths of a dosage form. The drug products containing the lower dose strengths should be compositionally proportional or qualitatively the same as the higher dose strengths and have the same release mechanism. For biowaivers, a dissolution profile should be generated and evaluated using one of the methods described under Section V in this guidance, "Dissolution Profile Comparisons." Biowaivers are generally provided for multiple strengths after approval of a bioequivalence study performed on one strength, using the following criteria: For multiple strengths of IR products with linear kinetics, the bioequivalence study may be performed at the highest strength and waivers of in vivo studies may be granted on lower strengths, based on an adequate dissolution test, provided the lower strengths are proportionately similar in composition [21 CFR 320.22(d)(2)]. Similar may also be interpreted to mean that the different strengths of the products are within the scope of changes permitted under the category "Components and Composition," discussed in the SUPAC-IR guidance.

SCALE-UP AND POSTAPPROVAL CHANGES (SUPAC)

After a drug product is approved for marketing by the FDA, the manufacturer may want to make a manufacturing change. The pharmaceutical industry, academia and the FDA developed (2, 3, 5, 3, 10, 3, 12–17) a series of guidances for the industry that discuss scale-up and postapproval changes, generally termed, SUPAC guidances (11). The FDA SUPAC guidances are for manufacturers of approved drug products who want to change 1) a component and composition of the drug product; 2) the batch size; 3) the manufacturing site; 4) the manufacturing process or equipment; and/or 5) packaging. These guidances describe various levels of postapproval changes according to whether the change is likely to impact on the quality and performance of the drug product. The level of change as classified by the FDA as to the likelihood that a change in the drug product might affect the quality of the product (Table 10).

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